Differences between surviving and non-surviving patients treated with levosimendan for acute myocardial ischemia

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Abstract

Introduction: Levosimendan, a calcium sensitizer and opener of ATP-dependent potassium channels, has positive inotropic, vasodilatory, and cardioprotective properties.
Method: 28 patients with acute myocardial infarction and/or cardiogenic shock (50%) scheduled for emergency surgical revascularization were treated with levosimendan in addition to catecholamines.
Results: 21 (75%) patients survived (SP), 7 (25%) patients died (NSP) within 30 days. Predicted mortality by logistic EuroSCORE for all 28 patients was 42±22%. Survivors had a lower ($p<0.05$) predicted mortality (35±17%) than the NSP (71±16%). SP were younger ($p<0.05$) (59±9 years) compared to NSP (71±8 years). Cardiac index was significantly higher in SP compared to NSP after cardiopulmonary bypass. An intraaortic balloon pump was inserted in 19% of the SP and in 71% of the NSP ($p<0.05$). Dialysis for renal failure was needed in 1 (5%) of the SP and in 2 (29%) of the NSP (n.s.). Surviving patients were ventilated for 26±20h, treated at the intensive care unit for 5.1±4.9 days, and dismissed from hospital after 15±19 days.
Conclusions: Surviving patients were younger, less severely ill and had fewer complications compared to non-surviving patients. Whether levosimendan is beneficial in patients with acute ischemia undergoing cardiac surgery must be answered by a prospective randomized trial.

Abbreviations

ACS:	acute coronary syndrome
CABG:	coronary artery bypass grafting
CPB:	cardiopulmonary bypass
IABP:	intra-aortic balloon pump
ICU:	intensive care unit
K_{ATP}-channel:	adenosine triphoshate-dependent potassium channel
PCI:	percutaneous coronary intervention
PDE-inhibitor:	phosphodiesterase inhibitor

Introduction

Every minute of delay in percutaneous revascularization for acute ST-elevation after myocardial infarction affected 1-year mortality (1). Therefore, all efforts should be made to shorten the total ischemic time in patients with acute coronary syndromes (ACS) to prevent cardiomyocyte apoptosis and to improve long term survival (1-4). Myocardial revascularization can be achieved either by fibrinolysis, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Emergency coronary artery bypass grafting (CABG) should be performed in patients with ACS when percutaneous intervention failed and/or pain and/or hemodynamic instability persist (5). In

these high-risk patients undergoing CABG cardioprotective strategies to prevent or attenuate apoptosis will improve short-term and long-term outcome. Reduction of myocardial damage is achieved by intraaortic balloon pulsation, assist devices, avoiding catecholamine induced cardiotoxicity, and preconditioning (2). Activation of mitochondrial and sarcolemmal adenosine triphoshate-dependent potassium (K_{ATP}) channels in cardiac myocytes is the main step of preconditioning and a potent cardioprotective mechanism (6).

Levosimendan is a calcium sensitzer with a unique dual mechanism of action. It exerts positive inotropic effects by binding calcium dependent to troponin C during systole only. It avoids an increase of intracardiomyocyte calcium (7,8). Levosimendan is also a potent opener of K_{ATP}-channels thus exerting cardioprotective and vasodilating effects. It reduced experimental infarct size and protected myocytes from apoptosis (9,10). Therefore, patients with ACS requiring inotropic support should benefit from the treatment with levosimendan. The primary objective of this retrospective analysis was to evaluate the differences between surviving and non-surviving patients undergoing emergency CABG treated with levosimendan for ACS.

Patients and methods

Between January 2005 and March 2007, a total of 28 patients with acute myocardial infarction requiring inotropic support were treated with levosimendan as "inoprotective" drug after approval of the institutional review board according to German legal practice (Landeskrankenhausgesetz Rheinland-Pfalz). After arrival in the operation theatre, the infusion of levosimendan was started as early as possible, always before cardiopulmonary bypass (CPB). A bolus of 6µg/kg levosimendan was infused within 15min followed by a continuous infusion of 0.2µg/kg/min (11). The infusion rate was halved to 0.1µg/kg/min if MAP was <60mmHg and norepinephrine was infused with a rate >0.5µg/kg/min and volume load was adequate. If hypotension persisted levosimendan was stopped. A goal directed hemodynamic therapy was started in all these critically ill patients parallel to the infusion of levosimendan. The hemodynamic goals to be achieved were cardiac index (CI) >2L/min/m^2 and mean arterial pressure (MAP) >60mmHg. When MAP decreased to less than 60 mmHg and right and left ventricular filling pressures (CVP, PCWP) were below 12 mmHg, colloids (hydroxy-ethylstarch, MW 130.000 Dalton) were infused. First choice positive inotropic drug, if levosimendan failed to increase CI >2L/min/m^2 was dobutamine up to 10µg/kg/min, second choice was epinephrine if dobutamine failed. Norepinephrine was used to increase MAP, if MAP was <60mmHg despite adequate CI and volume load. An intraaortic ballon pump was inserted if the hemodynamic goals (CI <2L/min/m^2 and MAP >60mmHg) were not achieved with adequate volume load, and with infusion of epinephrine <0.4µg/kg/min and norepinephrine <0.5µg/kg/min.

Hemodynamic monitoring consisted of a five lead ECG, radial or femoral artery cannulation, and a pulmonary artery catheter (PA) (7.0, Baxter, Irvine, CA) placed via right internal jugular vein. Heart rate (HR), MAP, central venous pressure (CVP), mean pulmonary artery pressure (MPAP), pulmonary capillary wedge pressure (PCWP), and cardiac output (CO) were measured. CO was measured using the mean of three values obtained by thermodilution technique (Explorer, Baxter, Irvine, CA). Cardiac index (CI), stroke volume (SV), systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) were calculated from standard formulae.

CPB was performed using mild hypothermia (core temperature 32.5-33.5° C), alpha stat, and nonpulsatile flow (2.4L/min/m^2). MAP was adjusted to 50 to 80 mmHg on CPB using vasopressors (norepinephrine) or vasodilators (nitroglycerin). Transfusion trigger was a hemoglobin level of <9.5g/L after CPB and <7.0g/L during CPB. Anesthesia was maintained as high dose sufentanil anesthesia (4-8µg/kg total dose). It was supplemented with midazolam (0.2-0.4mg/kg total dose) for hypnosis and pancuronium (0.15-0.3mg/kg total dose) for muscular paralysis. Sevoflurane could be used up to 0.8Vol% to the discretion of the anesthesiologist in charge of the case.

After surgery all patients were transferred to the intensive care unit (ICU). Controlled mechanical ventilation was continued in the ICU. FiO_2 and ventilation patterns were adjusted to keep paO_2 between 80 and 120mmHg and $paCO_2$ between 38 and 45mmHg. The alert patients were extubated when no major blood loss occurred and hemodynamic and respiratory parameters remained stable for at least 2h. Time to extubation was documented. No fast track procedures were performed in these high risk patients. Patients were discharged from ICU when they were in a stable hemodynamic situation with no inotropic or vasopressor support and in a stable respiratory situation (paO_2

>70mmHg with oxygen <4L/min via face mask) for more than 12h. Time to discharge from ICU and discharge from hospital were documented. Dialysis was initiated when serum creatinine increased >250µmol/L or oliguria <600ml/24h provoked fluid retention.

Creatinine kinase (CK) and creatinine kinase-myoglobin band (CK-MB) were measured using standard laboratory techniques preoperatively and postoperatively on arrival at ICU and at day 1, 2.

Following the accumulation of data, statistical models were formed and analyzed using MedCalc 4.30 statistical software (MedCalc Software, Mariakerke, Belgium). The Chi-square test was used for categorical univariate tests. Haemodynamics were analyzed using two-factorial analysis of variance (ANOVA) for repeated measurements. For significant findings, post hoc t-tests was applied at the end point of each measurement. In case of multiple comparisons, p values were corrected according to Bonferroni. Fisher`s exact test paired and nonpaired t-test were also used when appropriate. Results are expressed as mean ± standard deviation unless otherwise indicated.

Results

28 patients were enrolled between January 2005 and March 2007. Demographic data and preoperative EuroSCORE (12) are summarized in table 1. For all 28 patients, EuroSCORE was 13, 9-21 (median, range) with a predicted mortality of 42±22%. Mortality for all 28 patients included in the study was 25%. Surviving patients were younger, had a lower EuroSCORE, and a lower predicted mortality compared to non-surviving patients ($p<0.05$). 9 from 21 survivors were in cardiogenic shock on arrival in the operation room, and 5 from 7 in the non-survivors, (n.s.) respectively.

Peri-operative data are presented in table 2. Non-surviving patients had a longer time for surgery, CPB, and aortic crossclamping ($p<0.05$) compared to survivors. The number of arterial grafts did not differ, while non-survivors received significantly more vein grafts ($p<0.05$). All surviving patients could be weaned from CPB in the 1st attempt, while weaning from CPB in the 1st attempt failed in 3 of 7 non surviving patients ($p<0.05$). One patient died intraoperatively after 3 unsuccessful efforts to wean him from CPB. An IABP was inserted in 4 of 21 (19%) survivors and in 5 of 7 (71%) non-survivors, respectively ($p<0.05$). Dialysis for renal failure was needed in 1 (5%) survivor and in 2 (29%) non-survivors (n.s.). Survivors were ventilated for 25±20 hours postoperatively, while none of the non-surviving patients could be weaned from the ventilation. Length of stay at the ICU and in the hospital was significantly shorter in non-surviving patients compared to the survivors (table 3), as all non-surviving patients died within 6 days after the operation (Figure 1). In 4 survivors, levosimendan was stopped in the early postoperative period (4-9h) because of vasodilation and hypotension. In all other 24 patients, 12.5mg of levosimendan were infused.

Cardiac index (CI) did not differ between the survivors and non-survivors before CPB, but it was significantly higher in surviving patients after CPB compared to the non-survivors (Figure 2). Stroke volume

Table 1. Demographic data

	Survivors (n=21)	**Non-Survivors (n=7)**
Age (years)	59 ± 9	71 ± 8*
Height (cm)	173 ± 5	172 ± 9
Weight (kg)	81 ± 13	82 ± 15
Sex (Male/Female)	19/2	5/2
LVEDP (mmHg)	29 ± 11	30 ± 12
Cardiogenic Shock (%)	43	71
EuroSCORE (standard)	12; 9-17	17; 14-21*
Predicted mortality by logistic EuroSCORE (%)	30; 14-73	73; 45-90*

LVEDP, preoperative left ventricular enddiastolic pressure. All results are presented as mean ± standard deviation, except EuroSCORE (12) which is presented as median and range. * $p<0.05$ between survivors and non-survivors.

Table 2. Peri-operative data

	Survivors (n=21)	**Non-Survivors (n=7)**
Surgery (min)	140 ± 30	204 ± 53*
CPB (min)	65 ± 17	113 ± 42*
x-clamp (min)	34 ± 10	50 ± 26*
>1 weaning from CPB (%)	0	43*
Arterial grafts	0.9 ± 0.5	0.4 ± 0.7
Venous grafts	2.0 ± 0.7	2.9 ± 0.8*

Surgery: time needed from incision to last suture; CPB: cardiopulmonary bypass; x-clamp: aortic cross clamping; ; >1 weaning from CPB: more than 1 attempt was needed to wean the patient from cardiopulmonary bypass. All results are presented as mean ± standard deviation. * $p<0.05$ between survivors and non-survivors.

Table 3. Outcome

	Survivors (n=21)	Non-Survivors (n=7)
IABP (%)	19	71*
Dialysis (%)	5	29
LOS ICU (days)	5.1 ± 4.9	2.8 ± 1.9*
LOS hospital (days)	15.0 ± 19.0	3.9 ± 2.5*

IABP: intraaortic balloon pump; dialysis: need for dialysis; LOS ICU: length of stay at the intensive care unit (mean ± standard deviation); LOS hospital: length of stay at the hospital (mean ± standard deviation). *p<0.05 group levosimendan versus control group.

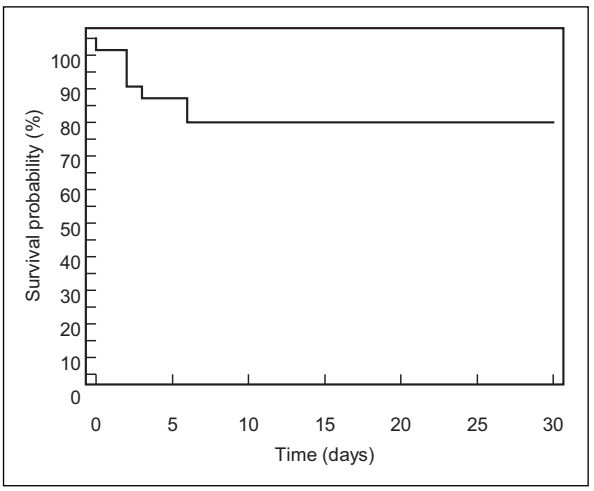

Figure 1. Survival of all patients in 30 days after the operation. Non-surviving patients died within 6 days after the operation.

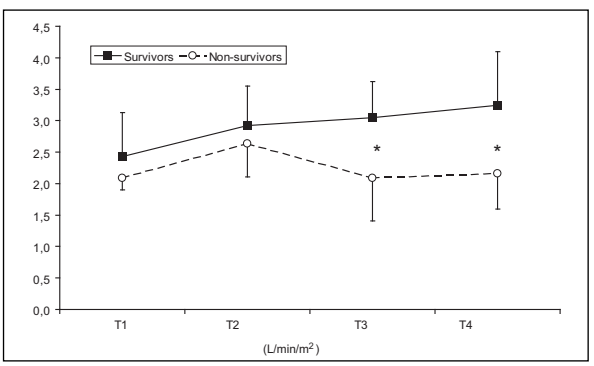

*Figure 2. Cardiac index after infusion of a bolus of levosimendan (6µg/kg body weight) (T1), 10 min before cardiopulmonary bypass (T2), 5min after cardiopulmonary bypass (T3) and at the end of surgery (T4). Closed line: surviving patients; dotted line: non-surviving patients. *p<0.05 between the two groups.*

(SV) was lower in the non-surviving patients compared to the surviving patients (table 4). Before CPB these differences of SV failed to reach statistical significance, while SV differed significantly between the 2 groups after CPB. CVP and PCWP were significantly lower at the end of surgery comparing survivors with non-survivors (table 4). The frequency of use of additional dobutamine (29% survivors; 29% non-survivors; n.s.), epinephrine (67% survivors; 100% non-survivors; n.s.), and norepinephrine (90% survivors; 100% non-survivors; n.s.) did not differ. The total amount of intraoperatively used dobutamine did not differ (11334±23955µg survivors; 7501±17948µg non-survivors; n.s.) between the 2 groups. The total amount of intraoperatively used epinephrine (1065±1192µg survivors; 6328±5639µg non-survivors; p<0.05) and norepinephrine (1962±1510µg survivors; 4895±2843µg non-survivors; p<0.05) was significantly increased in the non-surviving patients compared to the survivors. Sevoflurane was used in 13/21 (61.9%) surviving patients and in 4/7 (57.1%; n.s.) non-survivors.

CK and CK-MB were significantly lower in surviving patients compared to the non-survivors on day 1 and 2 after the operation (Figure 3).

Discussion

Emergency or urgent CABG should be considered in patients with acute coronary syndrome if PCI failed or if pain or hemodynamic instability persist after PCI and coronary anatomy is suitable for CABG (5). In these high risk patients cardioprotective strategies to prevent apoptosis and myocardial damage might improve short-term and long-term outcome. Activation of mitochondrial and sarcolemmal K_{ATP}-channels in cardiac myocytes is a strong cardioprotective mechanism (6,13). Activation of the K_{ATP}-channels can be achieved by ischemia or drugs, ischemic or pharmacologic preconditioning. Potassium channel openers of clinical interest are nicorandil and levosimendan (13). Levosimendan is a drug with a dual mechanism of action. First it binds calcium-dependent to cardiac troponin C (7,8). It increases myocardial contractility without increasing intramyocellular calcium thus avoiding the undesired side-effects of other positive inotropic drugs like increased oxygen consumption and an increased rate of arrhythmia. An interesting review on its positive inotropic effects was recently published by Toller and Stranz (14). Second levosimendan

Table 4. Hemodynamic data

Parameter	T1	T2	T3	T4	Group
HR(min^{-1})	91 ± 21	99 ± 26	103 ± 17*	109 ± 15	S
HR(min^{-1})	111 ± 17	125 ± 13	123 ± 13*	109 ± 14	NS
SV (ml)	55 ± 18	64 ± 18	60 ± 16*	59 ± 16*	S
SV (ml)	38 ± 6	46 ± 10	34 ± 13*	41 ± 15*	NS
MAP(mmHg)	67 ± 13	61 ± 16	59 ± 16	65 ± 17	S
MAP(mmHg)	68 ± 3	68 ± 7	55 ± 10	61 ± 7	NS
CVP(mmHg)	13 ± 5	11 ± 4	11 ± 4	12 ± 3*	S
CVP(mmHg)	13 ± 6	15 ± 5	14 ± 6	18 ± 2*	NS
MPAP(mmHg)	31 ± 8	26 ± 7	28 ± 6	27 ± 6	S
MPAP(mmHg)	31 ± 7	34 ± 3	29 ± 5	31 ± 8	NS
PCWP(mmHg)	19 ± 7	16 ± 5	16 ± 5	17 ± 4*	S
PCWP(mmHg)	19 ± 7	22 ± 7	21 ± 5	24 ± 6*	NS
SVR(dyn sec cm^{-5})	1030 ± 436	821 ± 285	727 ± 254	783 ± 291	S
SVR(dyn sec cm^{-5})	1097 ± 230	818 ± 334	886 ± 331	901 ± 395	NS
PVR(dyn sec cm^{-5})	204 ± 89	161 ± 71	160 ± 62	149 ± 72	S
PVR(dyn sec cm^{-5})	215 ± 77	228 ± 93	163 ± 35	144 ± 51	NS

S: surviving patients (n=21); NS: non-surviving patients (n=7); T1 after infusion of a bolus of levosimendan (6µg/kg body weight), T2 10 min before cardiopulmonary bypass (CPB); T3 5min after CPB; T4 end of surgery; HR: heart rate, SV: stroke volume; MAP: mean arterial pressure; CVP: central venous pressure; MPAP mean pulmonary arterial pressure; PCWP: pulmonary capillary wedge pressure; SVR: systemic vascular resistance; PVR: pulmonary vascular resistance, CI: cardiac index. All results are presented as mean ± standard deviation. #$p < 0.05$ from baseline value; *$p<0.05$ between the two groups.

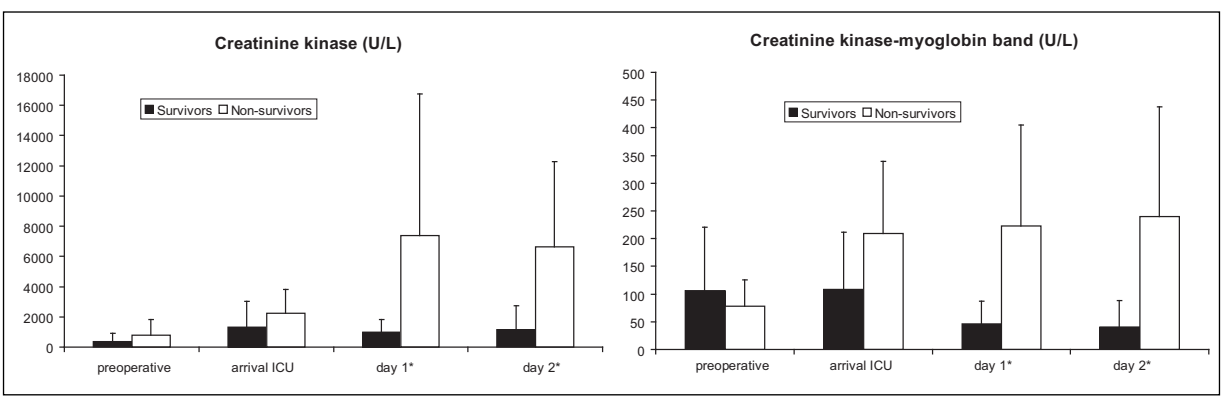

*Figure 3. Left side: creatinine kinase (U/L); right side: creatinine kinase-myoglobin band (U/L) preoperative, after the procedure on arrival at the intensive care unit, on day 1 after the operation and on day 2 after the operation. Black: surviving patients; white: non-surviving patients. *p<0.05 between the two groups.*

is a K_{ATP}-channel opener (13). In cardiac myocytes in culture, levosimendan at concentrations below the therapeutic range in humans opposed myocyte apoptosis (15). In dogs, levosimendan reduced experimental infarct size while simultaneously enhancing ventricular contractile function (9). These antiapoptotic and cardioprotective effects were blocked by inhibition of the K_{ATP}-channels (9,15). In patients with acute myocardial ischemia undergoing PCI, levosimendan improved the function of stunned myocardium (16). In human congestive heart failure, levosimendan was shown to exert anti-inflammatory, antioxidant, and antiapoptotic effects (17,18). In patients undergoing CABG, pre-treatment with levosimendan before CPB resulted in lower postoperative troponin I concentrations and a higher CI compared to the control group

(19). The authors concluded, that levosimendan reduced myocardial damage, suggestive of a preconditioning effect (19). These findings might explain the favorable long-term effects compared to dobutamine (19,20).

Interestingly, the patients dying in the study presented died within the first 6 days after the procedure. In the surviving patients, one patient required dialysis for renal failure. No multi-organ failure was seen in the group of surviving patients. K_{ATP}-channels are not specific for the heart, they are found in any organ of the whole body (21). In mice, levosimendan had marked protective effects against experimental endotoxemic renal failure (22). K_{ATP}-channel opening was reported to mediate hypoxic tubular injury (22). The LIDO-study (20) demonstrated a reduction in serum creatinine and markers of liver dysfunction compared to dobutamine in patients with low output heart failure.

In non-surviving patients myocardial damage might have been more intense than in non-surviving patients. This hypothesis is supported by the finding that the levels of CK and CK-MB were significantly increased on the 1st and 2nd postoperative day in non-survivors. Release of CK and CK-MB three or more times the upper limit of the reference range was associated with an increased mortality in 2,860 patients undergoing CABG (23). It is obvious that the amount of transmural necrosis is a major determinant of ventricular remodeling and function with an additional predictive value to infarct size (24). The infarct size is a major predictor of 30 day mortality (25). All reperfusion strategies intend to reduce myocardial damage, to limit infarct size, and to prevent myocardial necrosis.

Non-surviving patients were significantly older than surviving patients. Age >60 years was found to be a strong and continuously increasing risk factor for the predicted mortality of the logistic EuroSCORE (12). Despite the same treatment, CI was lower after CPB and an IABP was used more often in non-survivors. Surgery was more complex in non-surviving patients indicated by an increased number of vein grafts, increased time of CPB and aortic-crossclamping compared to surviving patients.

Several methodological issues have to be discussed with the data presented. The design of this observational study did not include a control group. With the observational data presented, levosimendan cannot be recommended for the treatment of acute myocardial ischemia in patients undergoing emergency CABG.

Early invasive revascularization in patients critically ill after acute myocardial infarction is still challenging. These patients are advanced in age and require a substantial amount of ICU resources and cardiothoracic surgical expertise (26). Whether a point of no return or a cut-off value for mortality should be defined or can de defined in this very specific patient population is a difficult problem which will not be solved by evidence based medicine alone. The data presented do not contribute to this question. The limited number of patients included in this observational study does not allow to calculate any specific risk factors for mortality and morbidity.

We conclude that in patients with acute myocardial ischemia undergoing emergency CABG, additional treatment with levosimendan did not increase mortality compared to the EuroSCORE database. Whether levosimendan is beneficial in patients with acute ischemia undergoing cardiac surgery must be answered by a prospective randomized trial. Surviving patients were younger, less severely ill, had a minor extent of myocardial damage, and had fewer complications compared to non-surviving patients.

Speculations

Levosimendan is a unique positive inotropic drug. It exerts positive inotropic effects without increasing intracellular calcium. Unlike catecholamines and PDE-inhibitors, it does not increase oxygen consumption and does not increase the rate of arrhythmias as side-effect. Levosimendan is a potent opener of the K_{ATP}-channels and it was shown to have cardioprotective effects.

Patients with acute ischemia requiring positive inotropic support might benefit from levosimendan as an “inoprotective drug”. In these patients, levosimendan protects from the deleterious effects of hypoperfusion, it does not worsen the metabolic balance of the ischemic heart and it protects cardiac myocytes from apoptosis.

However, before levosimendan can be recommended in these patients, a prospective randomized trial is urgently needed to prove or to reject the hypothesis of inoprotection.

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References

1. De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. Circulation 2004; 109: 1223-1225
2. Khoynezhad A, Jalali Z, Tortolani AJ. Apoptosis: pathophysiology and therapeutic implications for the cardiac surgeon. Ann Thorac Surg 2004; 78: 1109-1118
3. Lagerqvist B, Husted S, Kotny F, Stahle E, Swahn E, Wallentin L, Fast Revascularisation during InStability in Coronary artery disease (FRISC-II) investigators. 5-year outcomes in the FRISC-II randomised trial of an invasive versus a non-invasive strategy in non-ST-elevation acute coronary syndrome: a follow-up study. Lancet 2006; 368: 966-969
4. Fox KA, Poole-Wilson P, Clayton TC et al. 5-year outcome of an interventional startegy in non-ST-elevation acute coronary syndrome: the British Heart Foundation RITA 3 randomised trial. Lancet 2005; 366: 914-920
5. Acute Coronary Syndrome Guidelines Working Group. Guidelines for the management of acute coronary syndromes 2006. M J Aust 2006; 84 (8 Suppl): S9-S29
6. Gross GJ, Fryer RM. KATP channels and myocardial preconditioning: an update. Am J Physiol Heart Circ Physiol 2003; 285: H921-H930
7. Haikala H, Pollesello P. Calcium sensitivity enhancers. Idrugs 2000, 3: 1199-1205
8. Sorsa T, Heikkinen S, Abott MB et al. Binding of levosimendan, a calcium sensitizer, to cardiac troponin C. J Biol Chem 2001, 276: 9337-9343
9. Kersten JR, Montgomery MW, Pagel PS, Warltier DC. Levosimendan, a new positive inotropic drug, decreases myocardial infarct size via activation of K (ATP) channels. Anesth Analg 2000, 90: 5-11
10. Louhelainen M, Vahtola E, Kaheinen P et al. Effects of levosimendan on cardiac remodeling and cardiomyocyte apoptosis in hypertensive Dahl/Rapp rats. Br J Pharmacol 2007; 150: 851-861
11. Lehmann A, Lang J, Boldt J, Isgro F, Kiessling AH. Levosimendan in patients with cardiogenic shock undergoing surgical revascularization: a case series. Med Sci Monit. 2004;10: MT89-MT93
12. Roques F, Michel P, Goldstone AR, Nashef SA. The logistic EuroSCORE. Eur Heart J 2003; 24: 882-883
13. Pollesello P, Mebazaa A. ATP-dependent potassium channels as a key target for the treatment of myocardial and vascular dysfunction. Curr Opin Crit Care 2004; 10: 436-441
14. Toller WG, Stranz C. Levosimendan, a new inotropic and vasodilator agent. Anesthesiology 2006; 104: 556-569
15. Maytin M, Colucci WS. Cardioprotection: a new paradigm in the management of acute heart failure syndromes. Am J Cardiol 2005, 96, 26G-31G
16. Sonntag S, Sundberg S, Lehtonen LA, Kleber FX. The calcium sensitizer levosimendan improves the function of stunned myocardium after percutaneous transluminal coronary angioplasty in acute myocardial ischemia. J Am Coll Cardiol 2004; 43: 2177-2182
17. Avgeropoulou C, Andreadou I, Markantonis-Kyroudis S et al. The Ca2+-sensitizer levosimendan improves oxidative damage, BNP and pro-inflammatory cytokine levels in patients with advanced decompensated heart failure in comparison to dobutamine. Eur J Heart Fail 2005; 7: 882-887
18. Adamopoulos S, Parissis JT, Iliodromitis EK et al. Effects of levosimendan versus dobutamine on inflammatory and apoptotic pathways in acutely decompensated chronic heart failure. Am J Cardiol 2006; 98: 102-106
19. Tritapepe L, De Santis V, Vitale D et al. Preconditioning effects of levosimendan in coronary artery bypass grafting – a pilot study. Br J Anaesth 2006; 96: 694-700
20. Follath F, Cleland JG, Just H et al. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO-study): a randomised double-blind trial. Lancet 2002, 360: 196-202
21. Ardehali H, O'Rourke B. Mitochondrial K(ATP) channels in cell survival and death. J Mol Cell Cardiol 2005; 39: 7-16
22. Zager RA, Johnson AC, Lund S, Hanson SY, Abrass CK. Levosimendan protects against experimental endotoxemic acute renal failure. Am J Physiol Renal Physiol 2006; 290: F1453-F1462
23. Newall N, Oo A, Palmer N et al. Intermediate and high peri-operative cardiac enzyme release following isolated coronary artery bypass surgery are independently associated with higher one-year mortality. J Cardiothorac Surg 2006; 1: 20
24. Tarantini G, Razzolini R, Cacciavillani L et al. Influence of transmurality, infarct size, and severe microvascular obstruction on left ventricular remodeling and function after primary coronary angioplasty. Am J Cardiol 2006; 98: 1033-1040
25. Figueras J, Pena C, Soler-Soler J. Thirty day prognosis of patients with acute pulmonary oedema complicating acute coronary syndromes. Heart 2005; 91: 889-893
26. Delaney AP, Lee RP, Kay S, Hansen P. Early invasive revascularisation for patients critically ill after acute myocardial infarction: impact on outcome and ICU resource utilisation. Crit Care Resusc 2003; 5: 258-265

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